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BIODEGRADABLE INTRA VAGINAL DEVICES

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An intra vaginal device for delivering a pharmaceutical agent (e.g. progesterone) into a recipient mammal. The active agent is carried in a matrix of a biodegradable polymer (such as poly epsilon - caprolactone or a starch-like polysaccharide) having an ability to provide (without reliance on a supporting spine) desired retention characteristics of a variable geometry retention device, an appropriate release profile during a finite insertion period and biodegradability upon removal from the mammal.

Description of corresponding document:
WO9926556

Translate this text

BIODEGRADABLE INTRA VAGINAL DEVICES
The present invention relates to improvements in and/or relating to intra vaginal devices or inserts.

Our PCT/NZ97/00052 (published as WO 97/40776) discloses a variety of different forms of intra vagin:

device of a variable geometry type for retention within the intra vaginal cavity of an animal. Such devic hitherto have primarily involved the use of a silicone rubber composition which as a matrix has been impregnated with the active pharmaceutical agent (eg; progesterone). In the variable geometry type devi typified by the CIDRTM devices of this company the impregnated matrix has primarily been supported a spine of a resilient material such as nylon, the resilience of which is utilised for the variable geometry retention characteristics notwithstanding that such spine is usually fully overlaid with the impregnated matrix.

Various polymers possessing the ability to undergo biodegradation have been used to deliver pharmaceutical agents. A class ofpolymers possessing this characteristic and extensively utilized for the delivery of pharmaceutical agents are the polyesters.

Examples of these polymers include poly lactic acid, poly glycolic acid, poly(e- caprolactone) and vario co-polymers of lactide, glycolide ande-caprolactone.

Pharmaceutical products utilizing these polymers are typically formulated as microspheres, microcapsul films, rods or blocks. Retention within a body cavity has been achieved by a number of methods; the addition of dense fillers, injections or surgical implantation into muscle or subcutaneous area.

The present invention relates to a device or insert designed to deliver progesterone over an extended per oftime (2 to 20 days) upon insertion into the vagina of animals such as cattle, sheep, horses, pigs, goats, buffalo or deer. The device or insert is retained within the vagina by means of a flexible geometric arrangement (eg; of the arms and body).

Upon completion of treatment the device is removed and disposed of in a manner that preferably capitalizes upon the biodegradable properties of the polymer.

We have determined that biodegradable polymers typified bypoly(e-caprolactone) or a starch like saccharide can be appropriately impregnated with an intra vaginally effective active agent [such as progesterone (e.g. in concentration of from 5% to 70%wiw)] so as to provide appropriate in vivo release characteristics for the active agent over a period of intra vaginal retention required by the particular procedure whereupon, after extraction, the material is readily biodegradable following removal from the animal.

Surprisingly it has also been found that a polymer such as a poly (E-caprolactone) can be moulded notwithstanding its being impregnated with the active agent to provide not only the impregnated matrix also to provide the variable geometry device without an obligatory presence of a spine or the like such a in the prior art devices.

Similarly, starch like saccharides have been found to be capable of being shaped to the same effect.

Accordingly in a first aspect the present invention consists in a device or insert for insertion into the vag of a mammal, said device or insert consisting of a biodegradable polymer containing a pharmaceutical agent.

Preferably the device or insert is vaginally retainable (preferably by variable geometry means at least partially dependent on the resilience of the biodegradable polymer) for at least 5 days in a target species

Preferably the agent is progesterone in the concentration of 5 to 70% w/w.

Preferably the polymer is or includes poly (e-caprolactone).

Alternatively the polymer is or includes a starch-like polysaccharide.

In other forms the polymer may be a blend ofthe options and/or another polymer.

Preferably said biodegradable polymer includes therein both a cyclodextrin and an intra vaginally effect active ingredient.

The term "intra vaginally effective active agent" means any compound or composition or complex that l means of delivery into the vaginal cavity of a mammal can be absorbed systemically by the mammal therefrom so as to achieve or suppress some physiological effect. Examples include progesterone (eg: fc oestrus synchronisation and other purposes) and oxytocin (eg: for milk let down).

The term "cyclodextrin" includes any suitable cyclodextrin or mixtures thereof, eg: a-cyclodextrin,ss-cyclodextrin, y-cyclodextrin and hydroxypropyl P-cyclodextrin.

Preferably the cyclodextrin(s) comprise from 5 to 70% W/w
Preferably the absorption enhancing agent is hydroxypropyl P-cyclodextrin in the concentration of 5 to 70%W/wv
Preferably the device is of such geometry to facilitate retention in the vagina.

Preferably the agent does not appear as a fine powder or crystals upon the surface of the device.

In another aspect the present invention is an intra vaginal device or insert for a target species mammal comprising or including an intra vaginally insertable, retainable and removable mass of at least primaril one or both of poly(e-caprolactone) and a mouldable biodegradable starch-like polysaccharide, the mass virtue ofits resilience being of variable geometry which allows the intra vaginal insertion, retention and removal,
wherein said mass includes therein sufficient progesterone therein such that for a target species a blood serum level of progesterone of greater than2ng/m, for a period of at least 5 days can follow intra vaginal insertion thereof and wherein after removal the mass is biodegradable after removal from the animal.

Preferably said target species is selected from cattle, sheep, horses, pigs, goats, buffalo and deer.

Preferably said device or insert includes no supporting spine (eg; nylon or polyester).

Preferably the progesterone inclusion is sufficient to deliver progesterone for a period from 2 to 20 days

Optionally said mass may include cyclodextrin.

In a further aspect the present invention consists in the use or methods of use of such a device or any device of the present invention.

The present invention also consists in a method of manufacture of an intra vaginal device which results any device in accordance with the present invention.

In another aspect the invention consists in a method of manufacture of an intra vaginal device which comprises the step of including in a mouldable biodegradable polymer matrix both a cyclodextrin and a intra vaginally effective agent.

In still another aspect the invention consists in the use inter alia for animal group oestrus synchrony

purposes of devices or inserts of the present invention.

Preferably said use is intra vaginal use for a period of from 2 to 20 days and said device has a capability the target species mammal of providing for at least 5 days (if intra vaginally inserted for at least about 5 days) a blood serum level of progesterone of greater than2ng/m,.

Preferably all polymer(s) ofthe said mass (ifall, as is preferred, is to moulded) can be moulded without u of conditions prejudicial to the pharmaceutical agent and any cyclodextrin (or for that matter, any other absorption enhancing agent) present.

In still a further aspect the invention consists in a method of achieving with an animal (or group of animals) a blood serum level of progesterone of greater than 2ng/m, for a period of at least 5 days, said method comprising inserting and retaining in the or each animal for at least the at least 5 day period a device or insert ofthe present invention.

We have found that the biodegradable polymers of choice are capable of being effectively impregnated with the pharmaceutical agent and optionally an absorption enhancement agent, being effectively mould into the form of an intra vaginal device or insert of a kind reliant on variable geometry for retention, providing over the finite insertion period an appropriate tract to provide a desired pharmacological effec without detriment from any propensity of the polymer(s) to in vivo biodegrade, and, upon removal mucl lower in pharmaceutical agent content (see WO 97/40776),ofproviding no long term disposal problem owing to the propensity of the polymer(s) to biodegrade after removal from the animal.

Preferred forms of the present invention will now be described with reference to the accompanying drawings in which:
Figure 1 shows a device of variable geometry (the geometry being variable much in the way as discusse in WO 97/40776) but without a need for a spine of a dissimilar material (although if desired that can optionally be present),
Figure 2 shows an in vitro cumulative progesterone release against the squareroot-of-time (inserts manufactured from poly(e-caprolactone) (thin line) or silicone (thick line)).

Figure 3 shows an average plasma progesterone concentration against time following two rounds of vaginal treatment with a silicone insert of 134 cm2 surface area (s) or a poly(e-caprolactone) insert of 1(cm2 surface area(i), both of which contain 10%W/w progesterone (error bars are standard error means (12 for silicone inserts, n=9 for poly(e-caprolactone) inserts)),
Figure 4 shows a percentage of initial mass lost for drug-loaded(w) and blank (o) poly (e-caprolactone) inserts stored in compost over time (the solid line is the suggested mass loss as per promotional literatur supplied by the poly (e-caprolactone) manufacturer (error bars are ranges (n=2)),
Figure 5 shows a percentage of tensile performance lost for drug-loaded(-) andblank(n) poly(e-caprolactone) inserts buried in compost over time (the solid line is the suggested tensile performance los as per promotional literature supplied by the manufacturer. (Error bars are ranges (n=2)),
Figure 6 shows plasma progesterone concentration against time following vaginal treatment for 7 days with a silicone insert of 134 cm2 surface area(n), poly(- caprolactone) insert of 115 cm2 surface area (o) poly(e-caprolactone) with lactose insert of 115 cm2 surface area (o) (A final plasma sample was collecte 6 hours after removal on day 7. (Error bars are standard error means (n=3)), Figure 7 shows the percenta ofinitial mass lost for various poly (e-caprolactone) formulations stored in compost over time [Poly(e-caprolactone) (+), poly(e- caprolactone) with 10%WIw progesterone (w), poly (e-caprolactone) with 12.1%WIw lactose and 10.47%W/w progesterone (ç), poly(e-caprolactone) with 37.2%WIw P-cyclodextrin and 10.3%W/W progesterone (x), poly (e-caprolactone) with 43.8%WIw hydroxypropyl P· cyclodextrin and 10%WIw progesterone (*) or poly(e-caprolactone) with 39.9% W/w y-cyclodextrin an 9.7%W/w progesterone(w). (Error bars are ranges (n=2))], and

Figure 8 shows plasma progesterone concentration against time following vaginal treatment for 7 days with a Mater-Bi insert of 58 cm2 surface area with(w) or without(.)the addition of 20% w/w NaCl. (Erro bars are ranges (n=2)).

The choice of a resilient mouldable or shapable "polymer" which is biodegradable is such that degradati of the impregnated matrix (but with a low residual active ingredient loading) will occur over time after removal from the animal after having served its purpose during an intra vaginal insertionofpreferably fr 2 to 20 days (eg; about 7 days). Minimal degradation (if any) occurs during the period of insertion.

In the device of Figure 1 the device is wholly of the impregnated matrix which is poly(e-caprolactone) impregnated with progesterone in the concentration of 5 to 70% w/w without any solid active pharmaceutical agent appearing as a fine powder or crystals on the surface of the device.

In Figure 1 the wings 1 are resilient with respect to the body 2 and in an intra vaginal injection mode ca be reduced to a form or assume a position in an applicator in a known manner which facilitates insertior after which the resilience deploys the wings 1 to such condition as is required for retention. The resilien can be subsequently utilised to withdraw the device from within the vagina.

A suitable source of poly (e-caprolactone) is that product TONE767tom from Union Carbide Specialty Polymers and Products, Danbury, Ct, USA.

Starch-like polysaccharides that can likewise be impregnated and can be used for some or all of the devi includeMATER-Bi available from Novamont, Italy.

A preferred method of manufacturing of the device is as follows: Polymer polye-caprolactone, starch-lil polysaccharide or a blend of the two are mixed with active into a mixing vat using a suitable compound, eg; surfactant to adhere the active to the surface of the polymer granules or the use of compound extrud material.. The polymer/active mixture is then loaded into the hopper of an injection moulding machine, processed as a conventional thermoplastic, with machine set point parameters as per the technical recommendations of the polymer suppliers literature, and as per injection moulding standard practice.

Key processing set points forpoly e-caprolactone are: barrel temperatures ranging from 80 -1200C with injection pressure of 1600 bar. Total cycle time due to long cooling phase of approximately 55 seconds. Product is removed from the die and allowed to cool to equilibrium prior to packaging.

Preferably the performance of the device while inserted and its effect upon withdrawal is substantially a discussed in WO 97/40776 but with the advantages of(i) biodegradability after removal from the animal and (ii) the preferred omission of a spine of resilient material.

The preferred biodegradable polymers (typified by poly(-caprolactone) or a starch like saccharide) can b appropriately impregnated with an intra vaginally effective active agent such as progesterone (eg: in concentration of from 5% to 70% w/w) and an absorption enhancing agent such as hydroxypropyl P-cyclodextrin (eg: in concentrations of from 5% to 70% w/w) so as to provide appropriate release characteristics for the active agent over the period of intra vaginal retention.

The preferred device is wholly of the impregnated matrix which is poly(e- caprolactone) impregnated w hydroxypropyl P-cyclodextrin in the concentration of5 to 70% w/w.

A suitable source of hydroxypropyl P-cyclodextrin is that product BETA W7 HP available from Wacke Chemicals Australia, Victoria, Australia.

A preferred method of manufacture of the device is as follows: Polymer (poly(e- caprolactone), starch-li polysaccharide or a blend of the two) are mixed with active and absorption agent into a mixing vat. The polymer/active/absorption agent mixture is then loaded into the hopper of an injection moulding machin and processed as a conventional thermoplastic, with machine set point parameters as per technical recommendations of the polymers suppliers literature, and as per injection moulding standard practice. I processing points are: barrel temperatures ranging from 60 2500C with an injection pressure of 1600 ba Total cycle time due and allowed to cool to equilibrium prior to packaging.

Figure 1 shows a device of variable geometry (the geometry being variable much in the way as discusse in WO 97/40776) but without a need for a spine of a dissimilar material (although if desired that can optionally be present),
When inserts of the type shown in Figure 1 manufactured from poly(e- caprolactone) are subjected to ar vitro dissolution procedure to assess the release of progesterone they display release characteristics simi to the siliconeCIDRBTM insert, Figure 2.

Figure 2 shows an in vitro cumulative progesterone release against the squareroot-of-time. Inserts manufactured from poly(e-caprolactone) (thin line) or silicone (thick line).

When inserts of the type shown in Figure 1 manufactured from poly(e- caprolactone) of surface area les than the siliconeCIDRBTM inserts are administered to cattle and plasma samples collected for plasma progesterone concentration analysis slightly lower levels are observed, Figure 3.

Figure 3 shows an average plasma progesterone concentration against time following two rounds of vaginal treatment with a silicone insert of 134 cm2 surface area(z) or a poly(e-caprolactone) insert of 10 cm2 surface area("), both of which contain 10%W/w progesterone. Error bars are standard error means (12 for silicone inserts, n=9 for poly(e-caprolactone) inserts).

When inserts of the type depicted in Figure 1 manufactured from poly (ecaprolactone) which container progesterone at 10 %W/w or no progesterone are stored in compost for a period of 6 months the followi mass losses are observed, Figure 4.

Figure 4 shows a percentage of initial mass lost for drug-loaded(-) and blank (o) poly(-caprolactone) inserts stored in compost overtime. The solid line is the suggested mass loss as per promotional literatur supplied by the poly(e-caprolactone) manufacturer. Error bars are ranges (n=2).

When inserts of the type depicted in Figure 1 manufactured from poly (ecaprolactone) which contain progesterone at 10 %W/w or no progesterone are stored in compost for a period of6 months the followir tensile performance losses are observed,
Figure 5.

Figure 5 shows a percentage of tensile performance lost for drug-loaded(w) andblank(z) poly(e-caprolactone) inserts buried in compost over time. The solid line is the suggested tensile performance lo as per promotional literature supplied by the manufacturer. Error bars are ranges (n=2).

When inserts of the type shown in Figure 1 manufactured from poly(e- caprolactone) of surface area similar to our siliconeCIDR-B insert (disclosed in aforementioned WO 97/40776) are administered to cattle and plasma samples collected from plasma progesterone concentration analysis similar levels are observed. See Figure 6.

Figure 6 shows plasma progesterone concentration against time following vaginal treatment for 7 days with a silicone insert of 134 cm2 surface area("), poly(e- caprolactone) insert of 115 cm2 surface area(o

poly(e-caprolactone) with lactose insert of 115 cm2 surface area (o). A final plasma sample was collecte 6 hours after removal on day 7. Error bars are standard error means (n=3).

When inserts of the type depicted in Figure 1 manufactured from poly(e- caprolactone) which contain various excipients are stored in compost for a period of 6 months the mass losses shown in Figure 7 are observed.

Figure 7 shows the percentage ofinitial mass lost for various poly (e-caprolactone) formulations stored i compost over time. Poly (e-caprolactone)(#), poly (ecaprolactone) with 10%W/w progesterone (w), pol caprolactone) with 12.1%W/w lactose and 10.47%W/W progesterone(r), poly(e-caprolactone) with 37.2 W/w ss- cyclodextrin and 10.3%W/w progesterone (x), poly (e-caprolactone) with 43.8%W/w hydroxypropyl P-cyclodextrin and 10%W/w progesterone (*) or poly(e-caprolactone) with 39.9% W/w cyclodextrin and 9.7% w/w progesterone <RTI (-). Error bars are ranges (n=2).

When inserts are the type shown in Figure 1 manufactured using polysaccharide are administered to cat and plasma samples collected for plasma progesterone concentration analysis the levels of Figure 8 are observed.

Figure 8 shows plasma progesterone concentration against time following vaginal treatment for 7 days with a Mater-Bi insert of 58 cm2 surface area with(") or without(-) the addition of 20% w/w NaCl. Erro bars are ranges (n=2).

Claims of corresponding document: **WO9926556**

WHAT WE CLAIM IS: 1. A device or insert for insertion into the vagina of a mammal, said device or insert consisting of a biodegradable polymer containing a pharmaceutical agent.

2. A device or insert of claim 1 which is vaginally retainable for at least 2 days in a target species.

3. A device or insert of claim 1 or 2 wherein it is retainable by reliance on an ability to assume variable geometries some of which are dependent on the resilience of the biodegradable polymer.

4. A device or insert of claim 1 wherein the agent is progesterone.

4. A device or insert of claim 4 wherein the progesterone comprises from 5 to 70% W/w 5. A device or insert of claim 1 wherein the polymer is or includes poly (ecaprolactone).

7. A device or insert of claim 1 wherein the polymer is or includes a starch-like polysaccharide.

8. A device or insert of claim 7 or 8 wherein said biodegradable polymer includes therein both a cyclodextrin and an intra vaginally effective active ingredient
said intra vaginally effective active agent being any compound or composition or complex that by mean of delivery into the vaginal cavity of a mammal can be absorbed systemically by the mammal therefrom as to achieve or suppress some physiological effect.

9. A device or insert of any one of the preceding claims wherein said biodegradable polymer includes therein both a cyclodextrin and an intra vaginally effective active ingredient

said intra vaginally effective active agent being any compound or composition or complex that by mean of delivery into the vaginal cavity of a mammal can be absorbed systemically by the mammal therefrom as to achieve or suppress some physiological effect.

10. A device or insert of claim 9 wherein the cyclodextrin(s) comprise from 5 to 70W/w 11. A device or insert of any one of the preceding claims wherein the agent does not appear as a fine powder or crystals upon the surface.

12. An intra vaginal device or insert for a target species mammal comprising or including an intra vaginally insertable, retainable and removable mass of at least primarily one or both of poly (e-caprolactone) and a mouldable biodegradable starchlike polysaccharide, the mass by virtue of its resilien being of variable geometry which allows the intra vaginal insertion, retention and removal, wherein said mass includes therein sufficient progesterone therein such that for a target species a blood serum level of progesterone of greater than2"91 for a period of at least 5 days can follow intra vaginal insertion thereof and wherein after removal the mass is in vitro biodegradable.

13. A device or insert of claim 12 wherein said target species is selected from cattle, sheep, horses, pigs. goats, buffalo and deer.

14. A device or insert of claim 12 or 13 absent of any supporting spine.

15. A device or insert of any one of claims 12 to 14 wherein the progesterone inclusion is sufficient to deliver progesterone for a period from 2 to 20 days.

16. A device or insert of any one of claims 12 to 15 wherein said mass may include cyclodextrin.

17. The use or methods of use of a device or insert of any one of the preceding claims.

18. A method of manufacture of an intra vaginal device which results in a device or insert in accordance with any one of claims 1 to 11.

19. A method of manufacture of an intra vaginal device or insert which comprises the step of including : mouldable biodegradable polymer matrix both a cyclodextrin and an intra vaginally effective agent and thereafter forming the device or insert therefrom.

20. The use inter alia for animal group oestrus synchrony purposes of devices or inserts of any one of claims 1 to 16.

21. A use of claim 20 wherein said use is intra vaginal use for a period of from 2 to 20 days and said device has a capability in the target species mammal of providing for at least 5 days (if intra vaginally inserted for at least about 5 days) a blood serum level of progesterone of greater than2ng/m,.

22. A method of achieving with an animal (or group of animals) a blood serum level of progesterone of greater than 2ng/ml for a period of at least 5 days, said method comprising inserting and retaining in the each animal for at least the at least 5 day period a device or insert of any one of claims 1 to 16.

23. An intra vaginally device or insert substantially as hereinbefore described with reference to any one or more of the accompanying drawings.
